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A STUDY OF SERUM HEPATITIS FROM STORED PLASMA

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ABSTRACT

1. Preparing Institution: Department of Medicine, School of Medicine, University of Southern California, Los Angeles.

2. Title of Report: A Study of Serum Hepatitis from Stored Plasma

3. Principal Investigator: Allan G. Redeker, M.D., Assoc. Professor of Medicine

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A prospective controlled study of the frequency of hepatitis following the transfusion of pooled human plasma stored for six months in the liquid state at 30 - 32° Centigrade has been initiated. Surgical Service patients who receive only plasma and no other human blood products are the subjects of the study. The control solution, administered in a double-blind fashion, is five per cent human albumin solution. All patients allocated to the program are being followed in an identical manner, with clinical examinations and liver function studies at monthly intervals for a total of 180 days.

Forty-seven patients were allocated to the follow-up study program from February 1 to August 1, 1963. Two patients have completed 180 days of study without evidence of hepatitis. No evidence of hepatitis has been present to date in the other patients under study, except for one subject. This patient developed a mild, anicteric hepatic lesion with slight serum transaminase elevations, from which he has recovered. Liver biopsy revealed mild focal changes consistent with mild anicteric hepatitis.

A STUDY OF SERUM HEPATITIS FROM STORED PLASMA

PROGRESS REPORT

I. PURPOSE OF INVESTIGATION:

This project has been undertaken to determine the frequency of viral hepatitis following the transfusion of pooled human plasma stored for six months in the liquid state at 30-32° Centigrade.

II. DESIGN OF PROJECT:

A. Subjects and Place of Investigation:

The subjects of this investigation are patients from the Surgical Wards of the Los Angeles County Hospital, a hospital of approximately 4,000 beds. Only patients from the General Surgical Services, on one hospital floor are being used in this investigation. Patients judged by the ward physicians to need plasma are given plasma or a control solution according to a randomizing blind allocation scheme. Such recipients are then followed closely for 130 days following the transfusion of plasma or control solution.

B. Plasma:

The plasma being administered to patients on these surgical services is obtained by the Los Angeles County Hospital Blood Bank from Courtland Laboratories, Los Angeles, California. The specifications for its preparation include storage in the liquid state for six months at 30 to 32° C., and then lyophilization. The plasma is reconstituted by the ward physician immediately prior to its use. Plasma stored in the liquid state for a minimum of six months, but not lyophilized at the end of this period is not being used, since the storage times would be extremely variable from one unit to another.

C. Control Solution:

The control solution is human serum albumin, a five per cent isotonic solution with sodium added, packaged in a plasma-type bottle containing a total volume of 300 cc. Whereas the Los Angeles County Hospital is supplying the plasma

for this program, the Office of the Surgeon General, through this project, is purchasing the albumin solution and supplying it for patient administration at the Los Angeles County Hospital. The albumin solution is in the liquid state and is not lyophilized. This albumin solution is considered to be free of the hepatitis virus(es).

D. Distribution of Plasma and Albumin Solution:

The lots of plasma average approximately 180 units of plasma per lot. When a request for plasma is received from one of the surgical wards involved in this program, the plasma is supplied from that stocked by the Los Angeles County Hospital Blood Bank. The lot number of the dispensed plasma unit is recorded in the usual fashion for this hospital. Periodically, at times determined by the Project Statistician, only the albumin solution is available to fill the requests for plasma from the surgical wards. The period of time when only albumin solution is available is three and one-half days or some multiple thereof in length. The frequency of dispensation of the albumin control solution has been established prior to the initiation of this study, according to a scheme of randomization provided by the Project Statistician with the purpose of randomizing the allocation over a period of time and concealing the identification of the transfused material from the project personnel. During these periods of time, when a request for plasma is received from the surgical wards, it is filled instead with albumin solution and the lot number of the albumin solution is recorded in the usual fashion, but the word "albumin" does not appear on this record. The lot numbers of the plasma and albumin solution are recorded in three locations; at the plasma processing laboratory supplying these solutions, at the Los Angeles County Hospital Blood Bank, and at the Project Control Office. The recipients of both plasma and the control albumin solution are followed in an identical manner under this double-blind system. The key to the solution which each patient received

will not be broken until the termination of the project after the total data has been analyzed.

Personnel employed by this project make daily reviews of the Los Angeles County Hospital Blood Bank records for the dispensation of plasma (or albumin) and whole blood. Each patient who has received plasma (or albumin) is checked each day by personnel from this project, and the patient's medical record is reviewed daily. At the time of the patient's discharge from the hospital, or 23 days following initial plasma transfusion, whichever occurs first, the patient is considered for allocation to follow-up by the project, according to an allocation protocol. Patients are not allocated to follow-up by this project who have received blood during the current hospitalization, or who have received packed red blood cells or fibrinogen. Nor will patients be allocated who have a history of ever having received blood transfusions at any time in the past, nor will patients with a present or past history of liver disease be allocated for follow-up study.

E. Program for Patient Follow-Up:

Patients who meet the criteria for follow-up investigation as outlined in the project protocol are being examined at intervals of 23 days for a total period of 130 days following plasma or control solution transfusion. At the time of each 23 day period examination, the following biochemical procedures are performed: serum glutamic pyruvic transaminase (SGPT), serum glutamic oxaloacetic transaminase (SGOT), thymol turbidity, and total serum bilirubin. On the alternate four-week periods, halfway between the patient's clinic visits, the patient is contacted by telephone, at which time an inquiry is made according to a specific form regarding the patient's health. If either clinical or biochemical evidence suggesting acute viral hepatitis is found, the patient is re-examined at once, hospitalized, and a liver needle biopsy performed so that the diagnosis of acute viral hepatitis may be documented by the best possible means.

Sample units of each lot of plasma and of albumin solution used in this program are stored by this project for subsequent virologic and serologic examination, should hepatitis appear to develop from one of these lots. An addendum has recently been added to the original project protocol regarding action to be taken when a subject is found to develop acute viral hepatitis. In this event, the Project Statistician will be contacted by the Project Secretary and the Statistician will direct that the material the subject patient received be identified to him; that is, whether plasma or albumin and the lot number involved. The doctors doing the clinical follow-up on the patients will not be aware of this information. The Statistician will then direct that all recipients in this hospital of said plasma or albumin lot be listed and forwarded to him. He will cross-check against the patients currently under follow-up and eliminate the names from the list of those patients being followed on the project who have received this lot of plasma or albumin. He will then submit a list of co-recipients of this lot, minus the project patients being followed, to the Project Office. An attempt will then be made to follow-up, by whatever means are necessary, these co-recipients for evidence of hepatitis. In addition, information from the plasma processing laboratory will be obtained as to whatever medical units in the United States may have received part of the plasma or albumin lot in question. Attempts will be made to contact these other medical units regarding this same information.

III. IMPLEMENTATION OF PROJECT:

A. Arrangements have been made with the Los Angeles County Hospital system for the conduct of this project. Space for this project to conduct a weekly outpatient clinic has been provided. The Los Angeles County Hospital has agreed to make no charge for clinic visits by members of this project, if they should otherwise come under a part-pay category.

B. A contract has been arranged with the Los Angeles County Hospital General Chemistry Laboratory to perform all biochemical procedures necessary.

C. Permission has been granted by the Los Angeles County Hospital Medical Director and the chiefs of the surgical services of the University of Southern California and Loma Linda University to conduct this double-blind investigation of plasma and albumin solution on their services.

D. A contract has been made with a blood processing firm (Courtland Laboratories, Los Angeles, California) to supply to this project for use at the Los Angeles County Hospital the albumin solution as specified above; that is, a five per cent solution with added sodium, packaged in a plasma-type bottle. The surgical services have accepted this solution to be used in a double-blind fashion in lieu of plasma.

IV. SUMMARY OF RESULTS TO DATE:

Allocation of patients to follow-up by this project was initiated on February 1, 1963. The following results have been obtained to date (August 1, 1963):

1. Total number of patients from the general surgical services receiving plasma or albumin, and therefore coming to the attention of this project: 1,051
2. Total number of patients not eligible for allocation (death, blood transfusion, fibrinogen transfusion, history of previous blood transfusion, liver disease and/or other conditions): 395
3. Total number of patients allocated for follow-up study: 47
4. Total number of patients allocated for follow-up study but dropped from the program because of inability to be followed or development of a situation making them ineligible for follow-up: 14
5. Total number of patients with completed follow-up study (followed for 130 days): 2

6. Total number of patients currently being followed: 31

7. Number of clinic examinations completed by patients currently being followed:

Allocated, awaiting first clinic visit:	6
One Clinic visit:	11
Two clinic visits:	4
Three clinic visits:	5
Four clinic visits:	1
Five clinic visits:	3
Seven clinic visits:	1

Of the fourteen patients allocated to study by this project but dropped from follow-up, three patients were examined at one clinic visit, three patients were examined at two clinic visits, and one patient was examined at three clinic visits.

The number of patients allocated to follow-up study by this project each month has been as follows:

February	3
March	7
April	3
May	7
June	14
July	10

Two patients have completed the 180 day follow-up study period without evidence of hepatitis. Of the remaining patients currently under follow-up observation, evidence of hepatitis has to date been absent in all but one. This patient was a 24 year old Mexican man who had suffered multiple stab wounds of the chest in March of 1963. On March 17, 1963, an exploratory laparotomy was performed, but no abdominal injuries were found. He received at this time only plasma (or albumin solution), but specifically did not receive whole blood, and he did not receive Fluothane as an anesthetic. At his clinic visit in April, 1963, an SGOT of 63, SGPT of 78 and a thymol turbidity of 3 units were noted. The patient was asymptomatic and remained essentially so throughout the course of his illness. The total serum bilirubin never exceeded 0.3 mg.%. By May 16, 1963, the SGOT was 61 and the SGPT 157. The thymol turbidity at this time was 11 units. The serum

alkaline phosphatase, prothrombin time, and serum protein values were entirely normal. The patient had initially refused liver needle biopsy, but now accepted this procedure, which was performed on May 16, 1963. There was then a slow decline in the slightly elevated transaminase values, with all the values (SGOT, SGPT, thymol turbidity) finally reaching normal levels by July 11, 1963. On June 27, 1963, bromsulphalein retention was less than 5% after 30 minutes. The heterophile agglutination was negative. The liver biopsy specimen of May 16, 1963 revealed a rather heavy lymphocyte infiltration in the portal areas. There were a few small foci of accumulations of lymphocytes with parenchymal cells dropping out, but there was no lipochrome pigment in Kuppfer cells. A small amount of stainable iron was present in the Kuppfer cells. The parenchymal cells were not swollen and the sinusoids were only slightly dilated and discrete. This biopsy specimen was referred to Dr. Hans Popper at the Mount Sinai Hospital, New York, for review. Dr. Popper reported the specimen to represent a hepatitis without the earmarks of an etiology, and favored the tentative assumption of an anicteric viral hepatitis.

IV. PROJECTIONS FOR THE FUTURE:

During the initial organizational phases of this program, the allocation of acceptable patients for follow-up study was slow. This was frequently due to a number of local logistical factors which have been overcome, and it is expected that the recent higher rates of allocation will now continue. If not, additional surgical services will be incorporated into this program to supplement the number of patients available for follow-up study.

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